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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/728,716	11/30/2000	David F. O'Brien	15907-0022	4843

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EXAMINER
KISHORE, GOLLAMUDI S

ART UNIT	PAPER NUMBER
1615	8

DATE MAILED: 10/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/728,716	O'Brien
Examiner	**Art Unit**
Gollamudi Kishore	1615

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jul 8, 2002* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1 and 4-35* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1 and 4-35* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The amendment and the declaration filed on 7-8-02 are acknowledged.

Claims included in the prosecution are 1 and 4-35.

Claim Rejections - 35 USC § 102

1. **The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:**

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. **Claims 1, 4, 9-11, 16-17, 19, 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Lamparski (Biochemistry, vol. 31., 1992) of record.**

Lamparski discloses liposomes containing a phospholipid and a polymerizable colipid (note the abstract, Materials and Methods and Discussion). The polymerizable lipid upon polymerization with ultra-violet radiation polymerizes and destabilizes the liposomes thereby leaking the contents.

Applicant's arguments have been fully considered, but are not found to be persuasive for the following reasons. A careful examination of the specification appear to indicate that the lipids in both instant invention and in the prior art are dissolved in the organic solvent and formed into a film and then hydrated. Since the lipids are in a solution

form, one would expect the distribution of the lipids to be the same in both instances. Applicant has provided no experimental data to show the distribution is different in instant invention from that of the prior art. Furthermore, instant claims are composition claims and since the distribution of the lipids (whether random or discrete domain) is temperature dependent according to applicant, the distribution of lipids in the prior art preparations would be as 'discrete domains' below the room temperature; instant claims do not recite any temperature requirements. The examiner also points out in page 3109, col. 2 of Bennett (Biochemistry, 1995) which is already of record which appears to indicate that DOPE forms domains in bilayer membrane of liposomes.

The declaration of Dr. O'Brien has been carefully reviewed; it is not found to be persuasive for the following reasons. First of all, a declaration cannot overcome a 102 rejection. Secondly, what is shown and argued in the declaration are the differences between Lamparski's composition containing DOPC and bis-Sorb and instant composition containing DSPC and bis-Sorb; applicant also in this context point out to figure 2 in Lamparski. A careful examination of the figure 2 of Lamparski shows that Lamparski recognizes that the combination of DOPC and bis-Sorb does not show releases of calcein. What seems to be effective in the release according to Fig. 2 of Lamparski is the combination of DOPE and bis-Sorb. Therefore, a proper comparison would have been between Lamparski's DOPE-bis-Sorb combination with instant DSPC and bis-Sorb combination and not a composition containing DOPC which according to Lamparski is

ineffective in releasing calcein upon subjection to polymerization. Thirdly, applicant's comparison is made with compositions containing cholesterol and PEG derivatives of the lipids and instant independent claim does not recite the requirements of these two components. Finally, it is worth mentioning that the different results obtained with compositions containing either DOPC or DOPE appear to indicate that the release rates do not depend on lipid transition temperatures of DOPC (-20 degrees) and DOPE (-10 degrees) (see applicant's arguments with regard to random distribution and discrete domains which depend on the transition temperature).

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> **(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.**

4. Claims 1, 4-5, 9-11, and 16-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lamparski cited above.

The teachings of Lamparski have been discussed above. In essence, Lamparski teaches instant liposomes and the destabilizing effect of ultra-violet on the liposomal membrane. Although Lamparski does not teach a method of administration of a therapeutic agent of a diagnostic agent, based on the studies Lamparski suggests the applicability of the ionizing radiation induced destabilizing of the liposome and the

regulation of the release of the biological agents (note page 693). It would have been therefore, obvious to one of ordinary skill in the art to use the liposomes of Lamparski for the delivery of the diagnostic or therapeutic agents with a reasonable expectation of success since Lamparski provides guidance as to how to prepare the liposomes and suggests their use. Lamparski teaches only the of the application of ultraviolet radiation as the source as the ionizing radiation. However, in the absence of showing the criticality, it is deemed obvious to one of ordinary skill in the art to use any form of ionization as long as they polymerize the lipid.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant's arguments once again are based on the results obtained by Lamparski as noted from figure 2 and Table 1 and the amendment to instant claims. These arguments have been addressed above.

5. Claims 5-8, 12-15 and 34-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lamparski cited above in view of Woodle (BB, 1992) of record. Lamparski does not teach the inclusion of PEG in the liposomal composition.

Woodle discloses that the inclusion of hydrophilic polymers such as PEG in liposomes stabilizes the liposomes and also improves the circulation time of these sterically stabilized liposomes when administered (pages 180-185 and 194-195).

The inclusion of PEG in liposomes of Lamparski would have been obvious to one of ordinary skill in the art since such an inclusion stabilizes the liposomes and also improves their circulation time when administered.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant's arguments with regard to Lamparski have been discussed above. Applicant argues that Woodle discloses only certain sterically stabilized liposomes and that Woodle does not suggest the present invention. These arguments have not been found to be persuasive since Woodle teaches sterical stabilization of liposomes containing PEG-DSPE, PEG- DSPC, same lipids as claimed in instant claims 34 and 35 and the motivation to use PEG in liposomes. With regard to the declaration showing the different results obtained using DSPC:- instant specification on pages 36 and 37 (pointed out in the declaration) only report studies at 250 rads for composition 1 (containing DOPC) with a descriptive term, 'significant release'. It is unclear what the release rates are at 50 rads for this composition was and what the statistical levels of significance are.

6. **Claims 1, 4-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lamparski cited above by itself or in combination with Woodle also cited above, further in view of Hallahan (6,159,443) or vice versa.**

The teachings of Lamparski have been discussed above. In essence, Lamparski teaches instant liposomes and the destabilizing effect of ultra-violet on the liposomal membrane. Although Lamparski does not teach a method of administration of a

therapeutic agent of a diagnostic agent, based on the studies Lamparski suggests the applicability of the ionizing radiation induced destabilizing of the liposome and the regulation of the release of the biological agents (note page 693). It would have been therefore, obvious to one of ordinary skill in the art to use the liposomes of Lamparski for the delivery of the diagnostic or therapeutic agents with a reasonable expectation of success since Lamparski provides guidance as to how to prepare the liposomes and suggests their use. Lamparski teaches only the of the application of ultraviolet radiation as the source as the ionizing radiation and not other forms such as X-rays.

Hallahan discloses X-ray guided drug delivery to treat various neoplasms. The method involves administering the therapeutic agent or diagnostic agent in a delivery vehicle (liposomes) and irradiating the tissue using X-rays. The liposomes also contain antibodies attached to them. According to Hallahan such a method improves the drug delivery to the desired tissues (note the abstract, col. 1, line 61 through col. 6, line 58, col. 7, line 65 through col. 9, line 18, col. 15, line 18 through col. 17, line 9, col. 20, lines 6-49, col. 23, lines 10-59, Examples and claims).

The use of X-rays as the ionizing radiation with the liposomes of Lamparski would have been obvious to one of ordinary skill in the art since X-rays are not only another form of ionizing radiation to destabilize the liposomes in delivering the contents, but also provide an improved method of delivery when combined with delivery vehicles such as liposomes.

Alternately, to use the liposomes of Lamparski as the liposomes in Hallahan since Lamparski's liposomes release the active agent at the desired site when the X-rays polymerize the polymerizable lipid, thus providing an added advantage.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that Hallahan system does not involve polymerization of a colipid. This argument is not found to be persuasive since Hallahan is combined to show the use of X-rays as ionizing radiation for the release of active agent from liposomes to the selective tissue and the routine practice in the art of attaching antibodies to the surface of liposomes.

7. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *G.S. Kishore* whose telephone number is (703) 308-2440.

The examiner can normally be reached on Monday-Thursday from 6:30 A.M. to 4:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, T.K. Page, can be reached on (703)308-2927. The fax phone number for this Group is (703)305-3592.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [thurman.page@uspto.gov].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703)308-1235.

Gollamudi S. Kishore, Ph. D

Primary Examiner

Group 1600

gsk

October 16, 2002